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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/834,109	04/12/2001	Andrew H. Segal	11111/1185	5308

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EXAMINER
ZITOMER, STEPHANIE W

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 08/26/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/834,109	SEGAL ET AL.	
	Examiner	Art Unit	
	Stephanie Zitomer	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

P riod for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 June 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19 and 22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-19 and 22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Application status

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on June 19, 2003 has been entered.

Prosecution status

2. Rejections not reiterated herein from the previous Final Office Action mailed December 31, 2002 have been withdrawn in view of applicant's amendments and arguments. The arguments have been fully considered but are deemed moot where the rejections have been withdrawn.

Priority benefits

3. An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification or in an application data sheet (37 CFR 1.78(a)(2) and (a)(5)). The "specific reference" must include the status of each identified application. The specific reference to any prior nonprovisional application must include the relationship (i.e., continuation, divisional, or continuation-in-part) between the applications except when the reference is to a prior application of a CPA assigned the same application number.

Rejection under 35 U.S.C. 112, first paragraph: Lack of enablement

4. Claim 22 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for *in vitro* methods of use, does not reasonably provide enablement for *in vivo* methods. The claim is drawn to a method o gene therapy wherein the nucleic acid molecule of claim 1 or 2 comprising an aptamer and a nonaptameric biological effector sequence is introduced *in vitro* into a host cell whereby the effector sequence is internalized and the host cell is administered

to an organism. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate with *ex vivo* gene therapy encompassed by claim 22. There is no working example or description or even a prophetic example of the claimed aptamer covalently linked to a nucleic acid sequence comprising a "biological effector sequence" which, when introduced into an organism by the claimed invention method, effects a specific biological reaction. Examples of "biological effector sequences" include coding and antisense nucleic acids, nucleic acid enzymes and regulatory nucleic acids (page 14, first paragraph, followed by lists of prospective effector sequences). Working examples (pages 30-35) are prophetic with the exception of Example 6 in which antisense effector sequences were shown to inhibit expression of Enhanced Green Fluorescent Protein *in vitro* to a greater degree when conjugated to a human L-selectin aptamer than the aptamer alone. The specification is primarily directed to gene therapy of animals including humans (pages 27-29). However, at the time the application was filed, the prior art taught that gene therapy and antisense therapy were inoperative at worst and unpredictable at best. For example, Orkin et al. (1995) reviewed the state of the gene therapy art and reported that, among other problems, "[e]fficacy has not been established for any gene therapy protocol". Notably, in this regard, the specification describes dosage and administration in generalities (pages 28-29) but fails to provide any specific protocol for performing the claimed invention gene therapy methods. The Orkin et al. report also cited "the low frequency of gene delivery to target cells and the lack of definable biochemical or clinical endpoints". Notably, in this regard, the specification fails to identify any biochemical or clinical endpoints of the claimed invention methods. Administration of antisense oligonucleotides has been shown to have unexpected effects as reported in *Science* (Gura 1995). In one example wherein inhibition of B cell activity in culture was attempted the antisense oligonucleotides instead increased B cell activity. This report also cited side effects in animals administered antisense oligonucleotides including death in some instances. While the level of skill in the molecular biology art was high at the time of the

claimed invention, Ph.D. or higher, the level of unpredictability was also high as demonstrated by the cited references. Absent the required teaching and/or guidance in the specification, it is clear that the skilled practitioner in the art would have experienced undue experimentation in attempting to practice the claimed invention method of gene therapy comprising "introducing [*in vitro*] a biological effector sequence into a cell" and "administering said host cell to an organism" and that the disclosure is nothing more than an invitation to experiment. As the Courts have stated,

> A specification must be more than an invitation to experiment, i.e., applicant may not require persons skilled in the art to perform undue experimentation to achieve a successful result. See *In re Wright*, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); *In re Vaeck*, 947 F.2d 488, 495, 20 USPQ2d 1438, 1444 (Fed. Cir. 1933); *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

Response to applicant's arguments

5. Applicant's arguments filed June 19, 2003 have been fully considered but they are not persuasive. The arguments again attempt to limit the claimed invention to aptamers comprising "biological effector sequences" and methods for introducing/internalizing the aptamer while ignoring the "biological effector sequence" attached to the aptamer. The arguments allege that the enablement issue is not germane to the function/activity of the "biological effector sequence". If this is the case, it is suggested that "biological effector sequence" should be deleted from the claim. This argument contradicts the specification which is directed to *in vivo* methods at pages 20-22 and 27-29 and at page 14 specific genes are cited as effector sequences "useful for treating" specific diseases. Clearly, "treating" requires an effect of the "effector sequence". While it is agreed that the specification teaches the elements of making the claimed invention, it is pointed out that the specification does not teach how to practice the gene therapy encompassed by claim 22. The argument that applicant is not required under the law to enable each and every embodiment of the present invention" because [t]he Federal Circuit in *Atlas Powder* has held that claims may encompass some inoperative species..." is irrelevant to the enablement issue because the "biological

effector sequence" in the claims is **not** a species or even a single embodiment: it is the *sine qua non* of the claimed invention! The rejection for lack of enablement may be overcome by limiting claim 22 to *in vitro* usage by deleting the last phrase "and administering said host cell to the organism" and amending the preamble accordingly.

Rejections under 35 U.S.C. 112, second paragraph: Indefiniteness

6. Claims 1-19 and 22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

(a) The amended claims are confusing in being drawn to a product, a "nucleic aid molecule"' and reciting the method step, "wherein the aptamer binds to a cell surface molecule". It is suggested to recite a **property** of the aptamer as --specific for a cell surface molecule-- in view of the known property of aptamers that their sequences are specific for specific target molecules.

(b) Claims 3-6 lack antecedent basis in claim 1 or 2 for the "third nucleic acid sequence which is an aptamer" because its relationship to the first aptamer is not defined. It is suggested to clarify the function of the third aptamer.

(c) Claim 7 is confusing because the antecedent of "comprising DNA and RNA" is unclear. It is suggested to clarify which part of the nucleic acid molecule of claim 1 or 2 is DNA and which is RNA.

(d) Claim 18 is confusing due to improper Markush group language. It is suggested to recite --claim 1 **and** claim 2-- or, preferably, --a nucleic acid molecule of claim 1, a nucleic acid molecule of claim 2--.

Prior art of interest

7. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. The patent to George et al., 5,741,679, is cited for disclosure of a nucleic

acid molecule comprising a ligand-binding sequence and a regulatable ribozyme. The nucleic acid molecule is inserted into host cell via a vector.

Conclusion

8. The claims are free of the prior art of record but are rejected on other grounds.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephanie Zitomer whose telephone number is (703) 308-3985. The examiner can normally be reached on Monday through Friday from 9:00 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones, can be reached on (703) 308-1152. The official fax phone number for this Group is (703) 308-4242. The unofficial fax number is (703) 308-8724. The examiner's Rightfax number is 703-746-3148.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196. For questions and requests relating to formal matters contact LIE Chantae Dessau at 703-605-1237.

S. Zitomer

Stephanie Zitomer, Ph.D.

August 25, 2003

STEPHANIE W. ZITOMER
PRIMARY EXAMINER